Review Article

Open, hybrid or total minimally invasive esophagectomy; a comprehensive review based on a systematic literature search

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Abstract: Esophagectomy is the backbone of esophageal and gastroesophageal junction cancer with curative intention and the procedure is associated with significant risk for postoperative complications and mortality. Minimally invasive surgical techniques have been introduced with the aim to reduce morbidity and mortality. This review article has the objective to give an overview of the currently available evidence concerning the various techniques of minimally invasive esophagectomy (MIE) and their outcomes. A structured search of randomized controlled trials and large cohort studies published in the medical literature, comparing open and MIE techniques, was performed. Relevant studies were summarized, discussed and included in a comprehensive review based on the systematic literature search. MIE can be performed in various ways ranging from hybrid techniques to a totally minimally invasive approach. Increasingly also robotic surgical systems are being used. The published studies are somewhat ambiguous. Randomized trials report that MIE techniques are associated with a lower postoperative short-term morbidity and better short and medium term quality of life, compared to open esophagectomy (OE). Some population-based cohort studies suggest worse short-term outcomes after MIE. Most studies report long-term survival after MIE is at least similar to OE. The optimal surgical approach for esophageal cancer remains to be determined, but it is clear that MIE techniques will continue to develop and be an important part of treatment with curative intention in the future.

Keywords: Minimally invasive esophagectomy (MIE); robotic minimally invasive esophagectomy (RAMIE); hybrid minimally invasive esophagectomy (HMIE)

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Introduction

Esophagectomy is associated with high risk for postoperative complications compared to other types of surgery, and it is essential to establish the most favorable surgical approach in terms of short-term postoperative outcomes, long-term health-related quality of life (HRQOL) and survival.

In 1992 Sir Alfred Cuschieri in Dundee, Scotland, reported the first series of five successful thoracoscopically-assisted esophagectomies by performing thoracoscopy in prone position and then laparotomy in a three-stage approach similar to the open technique described by McKeown (1). Since then, a variety of minimally invasive esophagectomy (MIE) techniques have emerged. A range of hybrid techniques combining open surgery with some type of minimally invasive approach to a total minimally invasive procedure have been described over the years. Several types of positioning (prone, semi-prone, left lateral) during thoracoscopy as well as various approaches (two-stage,

three-stage) have been implemented. Additionally, in recent years robot-assisted MIE (RAMIE) has become increasingly popular.

In this review, we present a comprehensive summary of a systematic search of the published scientific literature and discuss the three main surgical approaches currently used; open esophagectomy (OE), totally minimal invasive esophagectomy (TMIE), and hybrid MIE (HMIE), including robot-assisted techniques.

Literature search

A literature search was conducted to identify relevant studies in PubMed, Web of Science, Embase and Cochrane. The following search terms were used: "esophagectomy", "esophagectomies", "minimally invasive procedures", "laparoscopy", "minimal*invasive", "minimal access", "minimal*surg", "minimal*surgical" or "hybrid". Inclusion criteria were: (I) studies published in English language, (II) randomized controlled trials (RCTs) or cohort studies (prospective and retrospective) comparing outcomes between OE, TMIE or HMIE. Uncontrolled case series were excluded. When duplicate studies were identified the most recent study was included.

The first search resulted in 918 articles. After a review of titles, abstracts, and in some cases full-text articles, 186 studies were chosen for review. In the second step, commentaries, case-reports, meta-analyses, and review articles were excluded, totaling 121 articles remaining (*Figure 1*). In a third step, RCTs, and large cohort studies were selected for final inclusion in the review. An additional study, published after the search, was added at the time the editing process took place. Details of the included studies are presented in *Table 1*.

OE versus MIE techniques in general

OE has been gold standard in the treatment of esophageal cancer for many years and is still a valid and effective treatment. However, a disadvantage with OE is the need for large surgical incisions including laparotomy in the upper abdominal midline and thoracotomy with concurrent traumatic rib spreading. MIE with video-assisted guidance offers several (at least theoretical) advantages including smaller incisions, magnification of the operative field and improved visual resolution, but relevant (clinical) benefits on the patient level remain unclear.

The studies referred to below report the results of comparisons between OE and a mix of HMIE and TMIE, which consequently makes the interpretation of the results more complex. In a British population-based study there was no difference in in overall morbidity or 30-day mortality between mixed MIE techniques and OE, while a higher reintervention rate was documented in the MIE group, which may to some extent be influenced by the learning curve for MIE (10). In a nationwide Japanese study better short-term outcomes, especially less respiratory complications, was reported after procedures with mixed MIE techniques compared to OE. There was also markedly less blood loss, but longer operation time and more reoperations after MIE, while there was no difference in postoperative mortality (12). In another Japanese population-based cohort study including 24,233 esophagectomies it was confirmed that MIE techniques were superior or at least equivalent to OE regarding postoperative morbidity and mortality (11). In an American study based on the National Cancer Data Base a significantly higher number of lymph nodes were retrieved using MIE techniques and a shorter hospital length of stay compared to OE. Tumor-free resection margins, readmissions, 30-day mortality and 3-year survival were similar between the groups and the study concluded that MIE for esophageal cancer was associated with improved perioperative outcome without compromising survival (3). A more recent study using the same database also confirmed that MIE appears to have equivalent oncological outcomes and survival when compared with the open approach (4) (*Table 1*).

OE compared to totally minimal invasive esophagectomy

There are a number of TMIE options. First, Ivor Lewis TMIE, which is considered technically challenging since the intrathoracic anastomosis must be performed thoracoscopically. This procedure is started with a laparoscopic gastric mobilization and abdominal lymph node dissection performed with the patient in supine position. Secondly, the patient is turned to either prone, semi-prone or left lateral decubitus position in order to gain thoracoscopic access in the right chest cavity. Another TMIE option, minimizing invasiveness even more, is transhiatal laparoscopic TMIE, mimicking open transhiatal esophagectomy, is performed with laparoscopic mobilization of the stomach and gastroesophageal junction followed by transhiatal dissection of the lower mediastinum, followed

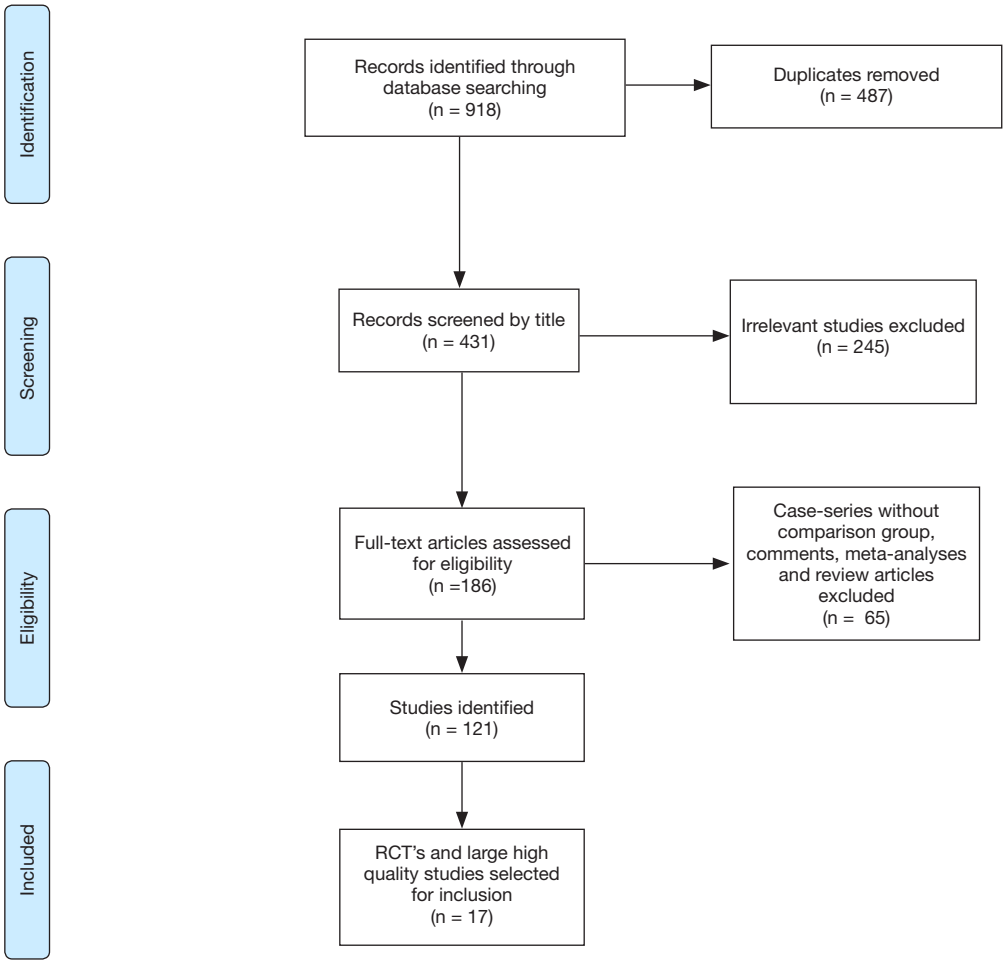

Figure 1 PRISMA flow diagram.

by a conventional left-sided cervical incision and an upper-midline mini laparotomy. The completion of the upper mediastinal dissection is usually accomplished by blunt manual dissection and use of so-called stripping technique, in the same manner as in open transhiatal esophagectomy. Lastly, the three-stage TMIE according to McKeown, was the first MIE technique that was popularized. The McKeown TMIE starts with thoracoscopic mobilization of the esophagus along with dissection of mediastinal lymph nodes with the patient in prone, semi-prone or left lateral decubitus position. The patient is then turned to supine position and laparoscopy with gastric mobilization and abdominal lymph node dissection is performed. The last step is a cervical incision through which the anastomosis between the proximal esophagus and the pulled-up gastric conduit is completed (20).

TMIE has been shown to be feasible for all patients regardless of age, tumor size and physiological fitness (21). The European multicenter TIME trial, was the first (relatively small) RCT to compare OE and TMIE. The study showed less pulmonary infections after surgery and shorter hospital stay in the TMIE group, while lymph node yield and R0 rate, were similar in both groups. At follow-up 6 weeks after surgery all aspects of HRQOL, with exception of the mental component, HRQOL was better among patients who had undergone TMIE compared to those after OE (8). Subsequent publications from this trial revealed a HRQOL advantage after TMIE at one year follow-up (7), while there was no significant difference in disease-free 3-year survival (19). A sub-study of the trial investigated the immunological changes after TMIE in comparison to OE and demonstrated significant differences, with lower leukocyte counts, IL-8, and prolactin at 1 week postoperatively in the TMIE group (9), suggesting reduced

Table 1 Summary data of included randomized clinical trials and population-based cohort studies comparing open and minimally invasive esophagectomy

Author/country	Year	Study type	Included patients	Exposure and measures	Findings
Mariette *et al.*/The Netherlands (2)	2019	Randomized controlled trial	207 esophagectomies between 2009–2012	HMIE compared to OE	Lower incidence of intraoperative and postoperative major complications in the HMIE group. Specifically, pulmonary complications were less in HMIE than OE
Yerokun *et al.*/ USA (3)	2016	Population-based analysis	For MIE, 1,077 patients underwent TMIE, and 231 patients underwent RAMIE	Perioperative outcomes and 3-year survival comparing MIE *vs.* OE *vs.* RAMIE	Patients with squamous cell carcinoma who underwent RAMIE had superior survival
Mitzman *et al.*/ USA (4)	2017	National Cancer Database	3,032 patients were included in the study, 2,050 underwent OE, 790 underwent MIE and 192 underwent RAMIE	Overall survival and perioperative mortality comparing OE to MIE and RAMIE	Mean lymph nodes examined were higher in the MIE group when compared to OE
Halpern *et al.*/ USA (5)	2019	National Cancer Database	306 patients who had undergone MIE and RAMIE were included in this study	Conversion to open surgery in patients undergoing MIE and RAMIE	82 of 1,487 (5.5%) RAMIE surgeries were converted to open, compared to 691 of 5,737 (12%) MIE procedures
Yun *et al.*/USA (6)	2020	Propensity score-weighted analysis	371 patients included 130 (35.0%) who underwent RAMIE, and 241 patients (65.0%) underwent OE	Comparison of the short- and long-term clinical outcomes	OE group had a higher incidence of pneumonia and a higher requirement of vasopressors and all-cause mortality was significantly higher in the OE group
Maas *et al.*/The Netherlands (7)	2015	Randomized controlled trial	115 patients were randomly assigned to receive either OE or MIE	Quality of life and late complications after MIE compared to OE	The results of quality of life at 1 year was better in the MIE group than in the OE group
Biere *et al.*/The Netherlands (8)	2012	Randomized controlled trial	115 patients were randomized to MIE or OE from five European centers, between June 2009 and March 2011	MIE *vs.* OE comparison for incidence of pulmonary infections, hospital stay and short-term HRQOL	Lower incidence of pulmonary infections, with a shorter hospital stay, and a better short-term quality of life in patients undergoing MIE
Maas *et al.*/The Netherlands (9)	2014	Randomized controlled trial, sub-study	27 esophagectomy patients	Investigate the immunological changes after MIE in comparison to OE	Significant differences was noticed between OE *vs.* MIE, in favor to MIE regarding leukocyte counts, interleukin-8, and prolactin at 1-week postoperatively
Mamidanna *et al.*/ England (10)	2012	Population-based study	7,502 esophagectomies between April 2005 to March 2010	Short-term outcomes after MIE and OE	No difference in 30-day mortality and overall morbidity between MIE *vs.* OE. The MIE group was associated with a higher reintervention rate

Table 1 (*continued*)

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Author/country	Year	Study type	Included patients	Exposure and measures	Findings
Yoshida *et al.*/ Japan (11)	2020	National Clinical Database	Analysis of 24,233 esophagectomies	MIE *vs.* OE	MIE was equivalent or superior to OE in terms of the incidence of the majority postoperative morbidities and surgery-related mortality
Takeuchi *et al.*/ Japan (12)	2017	National Clinical Database	9,584 patients who underwent esophagectomy between 2011–2012 were evaluated	Short-term outcomes of MIE with those who had underwent OE	Operative time was significantly longer in the MIE group. The MIE group had markedly less blood loss and required significantly less postoperative respiratory ventilation support
Kauppila *et al.*/ Sweden and Finland (13)	2018	Population-based study	A total of 1,614 patients, with 217 undergoing MIE *vs.* 1,397 OE between 2007 and 2014	Short-term outcomes after MIE *vs.* OE	Lower 90-day mortality for MIE *vs.* OE, shorter hospital stay, and lower 30-day readmission rates after MIE
Helminen *et al.*/ Sweden and Finland (14)	2019	Population-based study	209 patients underwent MIE and 1,430 underwent OE between 2007 and 2014	Anastomotic leak after MIE *vs.* OE	The need for repeated dilatation was higher after MIE compared to OE
Sihvo *et al.*/ Finland (15)	2019	Population-based study	A total of 590 esophagectomies, with patients undergoing MIE (n=159) or OE (n=431), between January 2004 and December 2014	Long-term outcome after OE *vs.* MIE	The results revealed that MIE is associated with improved long-term survival
Sihag *et al.*/ USA (16)	2016	National Database	3,708 esophagectomies performed between 2008 and 2011	Comparison of early surgical outcomes in MIE *vs.* OE	MIE is safe and with equivalent rates of morbidity and mortality as OE
Markar *et al.*/The Netherlands (17)	2020	Population-based study	115 patients from the TIME trial (59 OE *vs.* 56 OE) and 4,605 patients from the Dutch Upper GI Cancer Audit database (2,652 MIE *vs.* 1,953 OE)	Examine the external validity of the TIME trial with the help of the Dutch Upper GI Cancer Audit database	MIE was shown to have an increased rate of total pulmonary complications and reoperation rates
van der Sluis *et al.*/The Netherlands (18)	2019	Randomized controlled trial	112 patients randomized to receive either RAMIE or OE	RAMIE *vs.* OE	Overall, postoperative complications occurred less frequently with RAMIE, and RAMIE patients had better short-term functional recovery and quality of life at discharge
Straatman *et al.*/ The Netherlands (19)	2017	Randomized controlled trial	115 patients from 5 European centers between June 2009 and March 2011	Three-year MIE *vs.* OE survival	No differences in the 3-year survival for MIE and OE

OE, open esophagectomy; MIE, minimally invasive esophagectomy; RAMIE, robotic-assisted MIE; HRQOL, health-related quality of life.

inflammatory, and possibly less prominent immune system affection.

A recent Swedish-Finnish population-based study compared short-term outcomes following both Ivor Lewis and McKeown type TMIE and OE for cancer, and showed reduced 90-day mortality, shorter hospital stay, and lower 30-day readmission rates after TMIE compared to OE (13). In another population-based Swedish-Finnish study from the same group, the incidence of anastomotic strictures, comparing TMIE and OE, was reported, with a more frequent need for repeated dilatations after TMIE compared to OE (14).

In a comparative study between TMIE and OE based on the American Society of Thoracic Surgeons National Database from 2016, postoperative morbidity and mortality were equivalent between the groups, while TMIE was associated with longer procedure times, but shorter median length of hospital stay. As demonstrated in other studies, patients who underwent TMIE had higher rates of reoperation, while OE was associated with higher rates of wound infections, ileus and postoperative blood transfusions. High- and low-volume centers had similar outcomes. The longer procedure times and reoperations in TMIE may reflect a learning curve. The study concluded that TMIE is safe and with comparable morbidity and mortality as OE (16).

Few population-based studies have addressed long-term survival comparing TMIE and OE, but in a Finnish population-based study TMIE was associated with improved 5-year survival compared to OE, while in this study, there were no significant differences in 30- and 90-day mortality (15). In a very recently published study examining the generalizability of the TIME trial results to clinical practice, trial outcomes were compared to Dutch population-based DUCA registry data (17). There was a discordance between trial and population-based study groups: there was an increased risk for overall and pulmonary complications after MIE, while R0 resection rate and lymph node yield were higher and 30-day mortality lower after MIE (17).

In summary, the only randomized trial comparing OE *vs.* conventional, non-robotic, TMIE demonstrated that TMIE is associated with reduced risk for pulmonary infections, better short and medium term HRQOL, and similar number of resected lymph nodes, which in turn may be a proxy for improved or at least not compromised oncological outcomes. A large population-based cohort study is equivocal, and in some cases even suggests worse short term outcome after TMIE. TMIE is often associated with longer operation time and increased risk for reoperation, which may to some extent reflect the considerable learning curve.

HMIE *vs.* OE

The definition of HMIE is the combination of open and minimally invasive surgical techniques in the same procedure, i.e., laparoscopy combined with thoracotomy or laparotomy with thoracoscopy. Mainly Ivor Lewis esophagectomy, using laparoscopic and conventional open thoracotomy access, is performed with HMIE, as this enables open intrathoracic anastomosis, which has been one of the main obstacles in the TMIE Ivor Lewis learning curve. Several studies have shown laparoscopy to be associated with better postoperative respiratory functions, compared to laparotomy (22,23). It is well established that an upper midline laparotomy can significantly affect respiratory function to a degree similar as a thoracotomy, and the combination of both may therefore account for some of the significant morbidity reported after OE (24,25). Consequently the main hypothesis justifying HMIE has been that large surgical incisions on both sides of the diaphragm may be associated with increased risk for postoperative complications. Thus, the single compartment minimally invasive approach used in HMIE may reduce this risk (26). HMIE has been used at many centers during the introduction and development of TMIE.

The MIRO trial is a recently published RCT comparing HMIE to OE. Patients with esophageal cancer of the middle or lower third of the esophagus were included. The primary endpoint was intraoperative or postoperative complications within 30 days classified as Clavien-Dindo grade II or higher. In total, 207 patients were randomly assigned to HMIE or OE from October 2009 through April 2012. A total of 37 patients (36%) in the HMIE group had a Clavien-Dindo grade II or higher complication, compared with 67 (64%) patients in the OE group (odds ratio, 0.31; 95% confidence interval: 0.18 to 0.55; P<0.001). Major pulmonary complications were decreased after HMIE, 18% *vs.* 30% in the OE group. At three years, overall survival was 67% (95% CI, 57 to 75) in the HMIE group, compared with 55% (95% CI, 45 to 64) in the open-procedure group, which however did not reach statistical significance (2). HRQOL was significantly improved at 30 days after HMIE compared to OE, specifically role functioning and social functioning domains (27). The results of the MIRO trial are in accordance with most data from cohort studies comparing HMIE to OE (28).

In conclusion, the results of the only currently available published RCT and the published population-based cohort studies, quite unanimously report that HMIE is associated with significant improvements in short-term outcomes compared to OE, and that the oncological outcome of the procedure is at least as good as after OE.

RAMIE

The application of robot-assisted surgery is promising and has shown its potential to increase accuracy in dissection through improved maneuverability and visualization. The DaVinci robotic system has been widely implemented in the fields of urology, rectal cancer surgery, and gynecology. One main benefit is that the robotic arms can articulate, thereby improving dexterity compared to conventional laparoscopic instruments. These movements can closely mirror open surgical technique, with the important advantage of minimized surgical access trauma. Possible advantages with RAMIE compared to other MIE techniques, is yet to be clarified, especially with regard to justifying the increased cost associated with robotic, compared to conventional, minimally invasive surgery. These costs may in the future be shown to be offset by further decreases in blood loss, postoperative morbidity and length of hospitalization, compared to conventional MIE (29).

In a subgroup analysis of a population-based study, published in 2016, RAMIE was compared with MIE. The results showed no differences between RAMIE and MIE in tumor free resection margin, resected lymph nodes, hospital length of stay, 30-day readmission or 30-day mortality. Interestingly the study revealed that after stratification by histologic type, there were no significant differences in 3-year survival between MIE and RAMIE for patients with adenocarcinoma. However, patients with squamous cell carcinoma who underwent RAMIE were reported to have significantly better survival at 2 years (3).

In a study from 2019 factors associated with conversion to open surgery in patients undergoing MIE and RAMIE, and the impact of conversion to open surgery on postoperative outcomes, were analyzed. In total 5.2% of the RAMIEs were converted to open, compared to 12.0% in the TMIE group. Conversion rates decreased significantly for both approaches over the study period, indicating that the study period included the learning curve for both the procedure types. High volume of performed cases and robotic approach were associated with decreased conversion rates, indicating that RAMIE may have a shorter learning curve than conventional MIE. Patients who had undergone conversion to OE had an increased 90-day mortality, prolonged hospital stay, and higher rates of unplanned readmission (5). Short-term outcomes in a South Korean propensity score matched cohort study of RAMIE *vs.* OE in squamous cell carcinoma patients from 2019 showed that the OE group had a higher incidence of pneumonia, higher requirement of vasopressors postoperatively, more pain and worse short-term HRQOL scores. Regarding long term survival, interestingly, all cause mortality was higher and disease-free survival was lower in the OE group compared to RAMIE (6). Similar findings, with better outcomes with regard to lower blood loss, less postoperative pain, shorter length of stay, less intensive care time after RAMIE compared to OE, has been reported from other comparative cohort studies (30,31).

Recently the first RCT comparing RAMIE to OE, the ROBOT trial, was published. The ROBOT trial, which was a single center trial from Utrecht, with a design similar to the TIME trial, compared three stage McKeown RAMIE to three stage McKeown OE after randomization of 112 esophageal cancer patients (18). The trial was positive regarding the primary endpoint postoperative Clavien-Dindo II-V complications, with significantly lower incidence of 59% in the RAMIE group *vs.* 80% in the OE group (P=0.02). Functional recovery and short term HRQOL was also better after RAMIE (18).

In conclusion, early outcomes of RAMIE seem to be equivalent to MIE, and share its advantages compared to OE. The indications in some studies that RAMIE might be superior to MIE are so far not based on adequate data of sufficient quality, and needs to be evaluated in future studies.

Discussion

The majority of the studies included in this review indicate that minimally invasive surgical techniques are associated with improved outcomes in esophageal and gastroesophageal junction cancer treatment. This may to some extent be influenced by bias from residual confounding and case selection for MIE. Interestingly, there is a discrepancy between the results of the three randomized trials so far published, which all very clearly show better short-term outcome after MIE, and population-based data. The latter suggest the opposite, with more overall and pulmonary complications after MIE. This discrepancy may reflect the problems of generalizability that may hamper randomized trials, as they are often performed at expert

centers in a selected stratum of patients. The population-based studies are therefore an important complement and may reflect difficulties encountered in implementing complex new techniques in clinical practice outside selected high-volume centers.

Better short-term postoperative outcomes with reduced risk for respiratory complications and shorter length of hospital stay are important developments (8,12,13). The findings suggesting that MIE may be associated with increased numbers of resected lymph nodes and improved long-term survival (4,6,15,32) are promising, but still immature and need to be confirmed in large, well-designed population based studies, or ideally in a large, pragmatic multi-centric randomized phase III trial.

The negative aspects of MIE should also be highlighted. The procedure is complex and there is evidence that there is a long learning curve in the implementation of the technique (33) translated in higher risk for anastomotic leak and reoperation rates after MIE compared to OE (14).

A strength of this review is the focus on high-quality scientific evidence including only RCTs and comparative cohort studies. Limitations of the study include the relatively low number of RCTs in the field and the non-standardized reporting of postoperative complications after esophagectomy applied in most studies (34).

In conclusion, the available grade A evidence shows that minimally invasive surgical technique is associated with reduced postoperative morbidity and the MIRO trial even suggests that survival HMIE may be improved, compared to open surgery for esophageal and gastroesophageal junction cancer. However, the learning curve in the implementation of MIE needs to be addressed in order to avoid harm to patients when new surgeons and centers are introduced to the technique. RAMIE is a technical refinement of the MIE technique and future studies are needed if that refinement is associated with better outcomes in esophageal cancer treatment. The pursuit of better outcomes and lower mortality in the future will definitely include further implementation, and development of minimally invasive esophagectomy techniques.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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